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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/470,859	12/23/1999	ROY GEOFFREY SARGENT	A-68342-1/RM	6693

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EXAMINER

WOITACH, JOSEPH T

ART UNIT

PAPER NUMBER

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Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)
	09/470,859	Sargent et al.
	Examiner Joseph Woitach	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on Jan 18, 2003

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 41-45 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 41-45 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

4) Interview Summary (PTO-413) Paper No(s). _____

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

5) Notice of Informal Patent Application (PTO-152)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

6) Other: _____

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DETAILED ACTION

This application is an original application filed December 23, 1999, which claims benefit to provisional application 60/153,795, filed September 14, 1999.

Applicants amendment filed January 21, 2003, paper number 17 has been received and entered. Claims 1-37 and 39 have been canceled. Claims 41-45 have been added. Claims 41-45 are pending and currently under examination.

Specification

As noted in the previous office action, the disclosure is objected to because of the following informalities: On page 15, line 38, the specification refers to figure 13, however there is only two figures presented in the application

Additionally, the disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (for example page 9, line 2). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code throughout the complete disclosure. See MPEP § 608.01.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In Applicants' remarks it is noted that all the previous claims have been canceled and new claims are added. Newly added claims are now directed to a method of altering the nucleic acid of a mitochondria. It is noted that support for the independent claim amendments is found in claim 38 as originally filed. Further, it is noted that in response to the restriction requirement, Group I directed to altering a nucleic acid sequences of the nucleus or the mitochondria was elected (see paper number 5 for restriction groups and paper number 7 for response). Additionally, Applicants note that in the first office action, claims 38 and 40 were found free of the art of record (see office action mailed February 5, 2001, paper number 8, page 5). See Applicants amendment, page 2, second paragraph. Furthermore, in the same office action it is noted that methods of homologous recombination were indicated as enabled (see office action mailed February 5, 2001, paper number 8, pages 2-3). See Applicants amendment, page 2, third paragraph. Applicants note that the present claims do not recite nor encompass specific method steps which were specifically discussed in the basis of the rejection of record, and that the instant

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claims are enabled for practicing method and method steps as claimed. See Applicants amendment, page 2, fourth paragraph.

In response, it is noted that claims 38 and 40 were included in the enablement rejection. More specifically, in the basis of the rejection only the alteration of chromosomal sequences, not mitochondrial sequences, were indicated as enabled by the present disclosure. See office action mailed February 5, 2001, paper number 8, page 2. Further, the lack of the necessary guidance to practice the claimed method to affect mitochondrial sequences was specifically discussed. See office action mailed February 5, 2001, paper number 8, top of page 3. In response to the first office action, claims 38 and 40 were canceled without prejudice and without any specific argument in traverse of the original rejection, and the claims were amended to encompass altering DNA sequences of a donor nucleus (see Applicants amendment filed August 13, 2001, paper number 10). The claims under examination in subsequent office actions were directed specifically to altering ‘a preselected DNA sequence of *a donor nucleus* of a donor cell’ (*emphasis added*, claim 1). Contrary to Applicants comments, Examiner does not agree that the pending claims are enabled. In particular, the lack of the necessary guidance to practice the claimed method to affect mitochondrial sequences was specifically discussed in the first office action (see office action mailed February 5, 2001, paper number 8, top of page 3). Furthermore, subsequent rejections based on the breadth of the original claim as it was drawn to affecting mitochondrial DNA was not considered because the claims were amended to altering only

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nuclear DNA. The pending claims are now directed to subject matter which was indicated as not enabled in the first office action, and subsequently deleted by Applicants.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

As noted in the first office action, the present disclosure is silent with respect to any guidance for practicing the instantly claimed method in mitochondria. It is acknowledged that the mitochondria has a genome, however the membrane of the mitochondria is materially different from that of the cell or nucleus. The specification fails to provide the necessary

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guidance to practice the instantly claimed method because there is no guidance for introducing foreign DNA into the mitochondria. 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). The art teaches that homologous recombination can be affected in the nucleus of a cell, however there is no expectation that the artisan using the same methodology could extend the same methods for introducing DNA into a nucleus to physically and functionally different organelle such as the mitochondria. The specific mechanism of homologous recombination in the nucleus is not known, however it is important to note the nucleus of the cell contains many DNA repair enzymes and nuclear factors which are not present in the mitochondria. Further, the mechanisms of replication and maintenance of copy number is very different between the chromosomes of the cell and the mitochondrial DNA. Though the exact mechanisms of homologous recombination in the nucleus are not known, it is generally acknowledged in the art that factors present nucleus of the cell are required. Because the compliment of proteins present in the nucleus and mitochondria are different, there is no expectation that what is observed in the nucleus of a cell would naturally occur in the mitochondria.

Presently, even the presence of homologous recombination of endogenous sequences in the mitochondria is still a matter suspect in the art. In a review mitochondrial recombination, Eyre-Walker (2000) indicates that though not conclusive, population genetics of the non-clonality of mitochondria suggests that recombination in mitochondrial DNA may occur. (see

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summary in abstract). However, Wiuf (2001) in review of the methodology used by Eyre-Walker indicates that the use of various statistical methods affects ones conclusion and that more robust methodology is consistent with no recombination (see summary in abstract). Thus, at the time of filing and subsequently, the ability of the mitochondria to undergo homologous recombination of even endogenous sequences was unclear. In contrast to the mitochondria, recombination and crossing-over of nuclear sequences occurs quite frequently. Clearly the nucleus contains the factors required for homologous recombination whereas these factors are absent from the mitochondria. In light of these dramatic differences and absence of any concrete evidence that homologous recombination even occurs in the mitochondria, there is not expectation that what has been demonstrated to occur in the nucleus will occur in the mitochondria. Moreover, the specification is silent with respect to any specific methodology to practice the instantly claimed methods in the mitochondria.

With respect to using any recombinase encompassed by claim 41, the specification broadly indicates that any nucleoprotein is contemplated, however in the working examples in the instant specification only RecA is capable of generating the recombinant/targeted nuclei. As noted previously with respect to recombination in the nucleus there is no evidence of record that any other recombinase besides RecA would be functional or that endogenous recombinases would be functional. To the contrary, as pointed out in Applicants previous arguments, the introduction of only single-stranded polynucleotides results in 0% recombination (page 4), clearly suggesting that the endogenous recombinases present in the cell are incapable of

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incorporating any targeted polynucleotide. Importantly, there is no evidence of record that the activity of even RecA would extend to affecting recombination or alteration of a target sequence in the mitochondria. The Federal Circuit has stated that:

a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.**

(*Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1005 (CAFC 1997) (**emphasis added**)). It is noted that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). The high degree of unpredictability associated with the claimed method underscores the need to provide teachings in the specification that would provide the artisan with specific guidance to practice the method as claimed, however the specification does not provide such guidance and fails to provide any correlation between what was previously observed for the nucleus to the practice of the same methods in the mitochondria. Without such guidance in the specification and the lack of correlative working examples, the claims would require an undue amount of experimentation without a predictable degree of

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success on the part of the skilled artisan. The court has stated that “patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable”. The court continues to say that “tossing out the mere germ of an idea does not constitute an enabling disclosure” and that “the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement”. (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005).

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claim 41 is vague and unclear in the recitation of “a homology clamp” and the specific structure and nature of the complementary polynucleotides used in the method. Homology clamp is not specifically defined, however as set forth in the claim and

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throughout the present specification it is generally supported to be a sequence used to target the disruption/insertion of the polynucleotide. Claim 1 and dependent claims are unclear because the specification teaches that RecA recombinases (specifically set forth in claims 6-7) targets single stranded polynucleotides. Because the pair of polynucleotides used in the method are complementary, it is unclear if the complementary over the entire length of the polynucleotide, including the homology clamp (i.e. the homology clamp is double stranded) or if the homology clamp is represented as a single stranded tail wherein RecA could bind. Amending the independent claims to reflect the specific structure and nature of the polynucleotide which is introduced into the genome of the host cell, as well as amending dependent claims to be consistent with claim amendments, would obviate the basis of the rejection.

Conclusion

No claim is allowed. The claims are free of the art of record because the art fails to provide or make obvious enabled methods for altering the nucleic acid sequences of a mitochondria, however the claims are subject to other rejections.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP §

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706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Joseph T. Woitach

Deborah Crouch
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PRIMARY EXAMINER
GROUP 1632